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CLAIMS

What is claimed is:

1. A method of promoting a wild-type activity in a mutant form of a human protein of the p53 family, wherein one or more functional activities of said protein are at least partially impaired by the inability of said protein to maintain a functional conformation under physiological conditions, said method comprising the steps of:

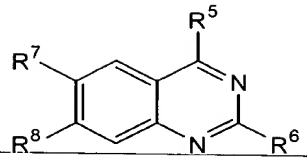
(a) contacting said mutant protein with an organic non-peptide compound that is capable of binding to one or more domains in said mutant protein under physiological conditions and stabilizing a functional conformation therein, and

(b) permitting said stabilized protein to interact with one or more macromolecules that participate in said wild type activity.

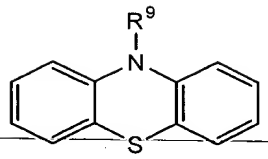
2. The method of claim 1 wherein said protein is selected from the group consisting of p53, p63, and p73.

3. The method of claim 2 wherein said protein is p53.

4. The method of claim 1, wherein said organic non-peptide compound is selected from the group consisting of:



(I)



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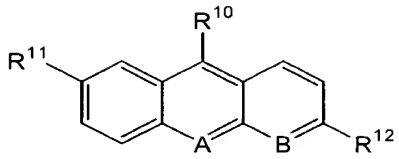
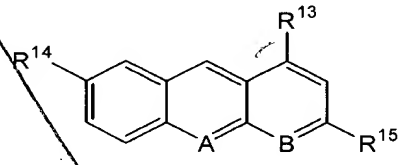
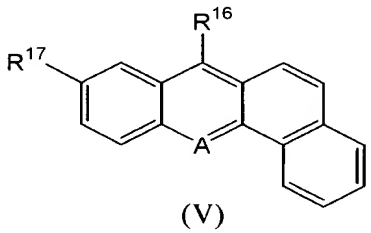


(III)



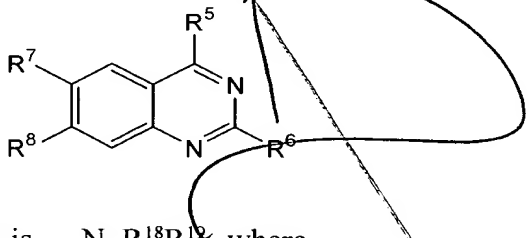
(IV)

and



(V)

wherein, for group I,



R^5 is $-N-R^{18}R^{19}$, where

R^{18} is H, $(C_1\text{-}C_6)$alkyl, or phenyl, and

R^{19} is H, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_{10})$cycloalkyl, or phenyl, wherein said alkyl, cycloalkyl or phenyl group is optionally substituted with hydroxy, $(C_3\text{-}C_8)$cycloheteroalkyl, $-CON\ R^{18}(CH_2)_pNR^{20}R^{21}$, $-(CH_2)_p\text{-}(CHR^{22})_m\text{-}(CH_2)_n\text{-}NR^{20}R^{21}$, or $-(CH_2)_p\text{-}(CHR^{22})_m\text{-}(CH_2)_n\text{-}NR^{20}R^{21}$, wherein p is 0-5, m is 0-5, n is 0-5, R^{22} is hydroxy or $(C_1\text{-}C_6)$alkyl, and

R^{20} and R^{21} are each, independently selected from:

(a) H, $(C_1\text{-}C_{12})$alkyl, $(C_3\text{-}C_{12})$cycloalkyl, $(C_3\text{-}C_{10})$heterocycloalkyl, $(C_6\text{-}C_{10})$aryl, $(C_5\text{-}C_9)$heteroaryl, $(C_1\text{-}C_6)$alkyl$(C_6\text{-}C_{12})$aryl, wherein said groups are optionally substituted by one or more hydroxy, halo, amino, trifluoromethyl, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$alkyl$(C_3\text{-}C_{10})$heterocycloalkyl, or $(C_1\text{-}C_6)$alkyl$(C_6\text{-}C_{10})$aryl; or

(b) $NR^{20}R^{21}$ taken together represent hydrogen, morpholine, or 4-$(C_1\text{-}C_6)$ alkylpiperizine;

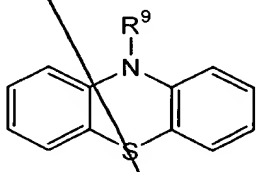
R^6 is

(a) $(C_1\text{-}C_6)$alkyl or $(C_2\text{-}C_8)$alkenyl, each optionally substituted by one or more phenyl groups, or

(b) phenyl substituted by halo, $(C_1\text{-}C_6)$alkoxy; and

R^7 and R^8 are the same, or different, and are selected from H, nitro, $(C_1\text{-}C_6)$alkoxy, or halogen selected from fluoro, chloro, and bromo;

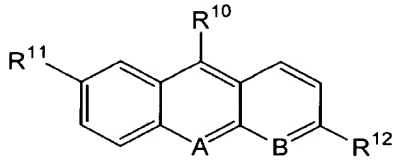
wherein, for group II,



R^9 is $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_{10})$cycloalkyl, or phenyl, wherein said alkyl, cycloalkyl or phenyl group is optionally substituted with hydroxy, $(C_3\text{-}C_8)$cycloheteroalkyl, $-CON R^{18}(CH_2)_pNR^{20}R^{21}$, $-(CH_2)_p\text{-}(CHR^{22})_m\text{-}(CH_2)_n\text{-}NR^{20}R^{21}$, or $-(CH_2)_p\text{-}(CHR^{22})_m\text{-}(CH_2)_n\text{-}NR^{20}R^{21}$, wherein p is 0-5, m is 0-5, n is 0-5, R^{22} is hydroxy or $(C_1\text{-}C_6)$alkyl, and

R^{20} and R^{21} are each independently selected from H, $(C_1\text{-}C_{12})$alkyl, $(C_3\text{-}C_{12})$cycloalkyl, $(C_3\text{-}C_{10})$heterocycloalkyl, $(C_6\text{-}C_{10})$aryl, $(C_5\text{-}C_9)$heteroaryl, $(C_1\text{-}C_6)$alkyl$(C_6\text{-}C_{12})$aryl, wherein said groups are optionally substituted by one or more hydroxy, halo, amino, trifluoromethyl, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$alkyl$(C_3\text{-}C_{10})$heterocycloalkyl, $(C_1\text{-}C_6)$alkyl$(C_5\text{-}C_9)$heteroaryl, or $(C_1\text{-}C_6)$alkyl$(C_6\text{-}C_{10})$aryl;

wherein, for group III,



R^{10} is $-N-R^{18}R^{19}$, where

R^{18} is H, $(C_1\text{-}C_6)$alkyl, or phenyl, and

R^{19} is H, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_{10})$cycloalkyl, or phenyl, wherein said alkyl, cycloalkyl or phenyl group is optionally substituted with hydroxy, $(C_3\text{-}C_8)$cycloheteroalkyl, $-CON R^{18}(CH_2)_pNR^{20}R^{21}$, $-(CH_2)_p\text{-}(CHR^{22})_m\text{-}(CH_2)_n\text{-}NR^{20}R^{21}$, or

$-(CH_2)_p-(CHR^{22})_m-(CH_2)_n-NR^{20}R^{21}$, wherein p is 0-5, m is 0-5, n is 0-5, R^{22} is hydroxy or (C_1-C_6)alkyl, and

R^{20} and R^{21} are each, independently selected from:

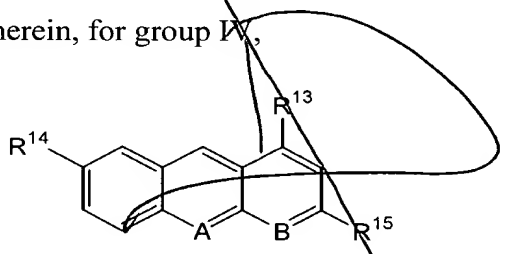
(a) H, (C_1-C_{12})alkyl, (C_3-C_{12})cycloalkyl, (C_3-C_{10})heterocycloalkyl, (C_6-C_{10})aryl, (C_5-C_9)heteroaryl, (C_1-C_6)alkyl(C_6-C_{12})aryl, wherein said groups are optionally substituted by one or more hydroxy, halo, amino, trifluoromethyl, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)alkyl(C_3-C_{10})heterocycloalkyl, (C_1-C_6)alkyl(C_5-C_9)heteroaryl, or (C_1-C_6)alkyl(C_6-C_{10})aryl; or

(b) $NR^{20}R^{21}$ taken together represent hydrogen, morpholine, or 4-(C_1-C_6) alkylpiperizine;

A and B are the same or different, and each represents carbon or nitrogen; and

R^{11} and R^{12} are the same, or different, and are selected from H, nitro, (C_1-C_6)alkoxy, or halogen selected from fluoro, chloro, and bromo;

wherein, for group IV,



R^{13} is $-N-R^{18}R^{19}$, where

R^{18} is H, (C_1-C_6)alkyl, or phenyl, and

R^{19} is H, (C_1-C_6)alkyl, (C_3-C_{10})cycloalkyl, or phenyl, wherein said alkyl, cycloalkyl or phenyl group is optionally substituted with hydroxy, (C_3-C_8)cycloheteroalkyl, $-CON\ R^{18}(CH_2)_pNR^{20}R^{21}$, $-(CH_2)_p-(CHR^{22})_m-(CH_2)_n-NR^{20}R^{21}$, or $-(CH_2)_p-(CHR^{22})_m-(CH_2)_n-NR^{20}R^{21}$, wherein p is 0-5, m is 0-5, n is 0-5, R^{22} is hydroxy or (C_1-C_6)alkyl, and

R^{20} and R^{21} are each, independently selected from:

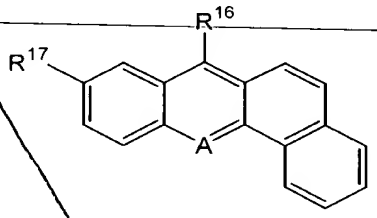
(a) H, (C_1-C_{12})alkyl, (C_3-C_{12})cycloalkyl, (C_3-C_{10})heterocycloalkyl, (C_1-C_6)alkyl(C_5-C_9)heteroaryl, (C_5-C_9)heteroaryl, (C_6-C_{10})aryl, and (C_1-C_6)alkyl(C_6-C_{10})aryl, wherein said groups are optionally substituted by one or more hydroxy, halo, amino, trifluoromethyl, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)alkyl(C_3-C_{10})heterocycloalkyl, (C_1-C_6)alkyl(C_5-C_9)heteroaryl and (C_1-C_6)alkyl(C_6-C_{10})aryl; or

(b) $NR^{20}R^{21}$ taken together represent hydrogen, morpholine, or 4-(C_1-C_6) alkylpiperizine;

A and B are the same or different, and each represents carbon or nitrogen; and

R^{14} and R^{15} are the same, or different, and are selected from H, nitro, $(C_1\text{-}C_6)$alkoxy, or halogen selected from fluoro, chloro, and bromo; and

wherein, for group V,



A is carbon or nitrogen;

R^{16} is $-N-R^{18}R^{19}$, where

R^{18} is H, $(C_1\text{-}C_6)$alkyl, or phenyl, and

R^{19} is H, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_{10})$cycloalkyl, or phenyl, wherein said alkyl, cycloalkyl or phenyl group is optionally substituted with hydroxy, $(C_3\text{-}C_8)$cycloheteroalkyl, $-CON\ R^{18}(CH_2)_pNR^{20}R^{21}$, $-(CH_2)_p\text{-}(CHR^{22})_m\text{-}(CH_2)_n\text{-}NR^{20}R^{21}$, or $-(CH_2)_p\text{-}(CHR^{22})_m\text{-}(CH_2)_n\text{-}NR^{20}R^{21}$, wherein p is 0-5, m is 0-5, n is 0-5, R^{22} is hydroxy or $(C_1\text{-}C_6)$alkyl, and

R^{20} and R^{21} are each, independently selected from:

(a) H, $(C_1\text{-}C_{12})$alkyl, $(C_3\text{-}C_{12})$cycloalkyl, $(C_3\text{-}C_{10})$heterocycloalkyl, $(C_6\text{-}C_{10})$aryl, $(C_5\text{-}C_9)$heteroaryl, $(C_1\text{-}C_6)$alkyl$(C_6\text{-}C_{10})$aryl, and $(C_1\text{-}C_6)$alkyl$(C_5\text{-}C_9)$heteroaryl, or wherein said groups are optionally substituted by one or more hydroxy, halo, amino, trifluoromethyl, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$alkyl$(C_3\text{-}C_{10})$heterocycloalkyl, $(C_1\text{-}C_6)$alkyl$(C_5\text{-}C_9)$heteroaryl, or $(C_1\text{-}C_6)$alkyl$(C_6\text{-}C_{10})$aryl; or

(b) $NR^{20}R^{21}$ taken together represent hydrogen, morpholine, or 4-$(C_1\text{-}C_6)$ alkylpiperizine; and

R^{17} selected from H, nitro, $(C_1\text{-}C_6)$alkoxy, or halogen selected from fluoro, chloro, and bromo.

5. The method of Claim 1 wherein said organic non-peptide compound binds to the DNA binding domain, residues 94 to 312, of human p53 protein.

6. The method of claim 5 wherein the DNA binding domain of said p53 protein comprises a missense mutation at an amino acid position selected from the group consisting of residues 143, 173, 175, 241 and 249.

7. The method of claim 1 wherein steps (a) and (b) are performed simultaneously.

8. The method of claim 1 wherein steps (a) and (b) are performed sequentially.

9. A method of treating a human subject for a disease state associated with possession of a mutant protein of the p53 family having one or more diminished wild-type activities, comprising the steps of:

(a) administering to said subject an organic non-peptide compound that is capable of binding to one or more domains in said mutant protein under physiological conditions, and stabilizing a functional conformation therein, and

(b) permitting said stabilized protein in said patient to interact with one or more macromolecules that participate in said wild-type activity.

10. The method of claim 9 wherein said protein is selected from the group consisting of p53, p63 and p73.

11. The method of claim 10 wherein said protein is p53.

12. The method of Claim 10 wherein said organic non-peptide compound binds to the DNA binding domain, residues 94 to 312, of human p53 protein.

13. The method of claim 12 wherein the DNA binding domain of said p53 protein comprises a missense mutation at an amino acid position selected from the group consisting of residues 143, 173, 175, 241 and 249.

14. The method of claim 9 wherein steps (a) and (b) are performed simultaneously.

15. The method of claim 9 wherein steps (a) and (b) are performed sequentially.

16. The method of claim 10 wherein said disease state is cancer.

17. A method of treating a human subject for cancer comprising the steps of:

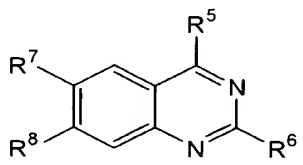
(a) administering to said subject an organic non-peptide compound that is capable of binding to one or more domains of a human protein of the p53 family under physiological conditions, and stabilizing a functional conformation therein, and

(b) permitting said stabilized protein to interact with one or more macromolecules that participate in a wild-type activity of said protein.

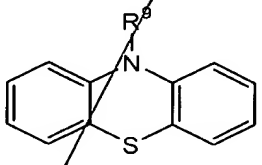
18. The method of claim 17 wherein said protein is selected from the group consisting of p53, p63, and p73.

19. The method of claim 17 wherein said protein is p53.

20. The method of claim 17, wherein said organic non-peptide compound is selected from the group consisting of:



(I)



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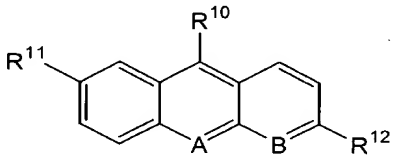

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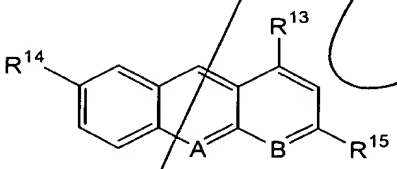
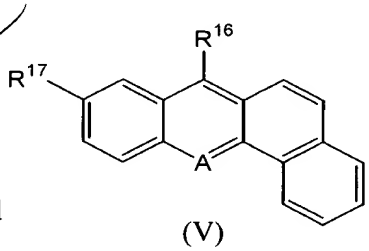


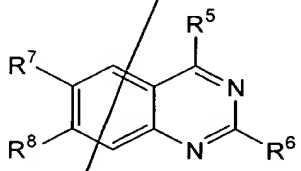
(IV)

and



(V)

wherein, for group I,



R^5 is $-N-R^{18}R^{19}$, where

R^{18} is H, $(C_1$-$C_6)$alkyl, or phenyl, and

R^{19} is H, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_{10})$cycloalkyl, or phenyl, wherein said alkyl, cycloalkyl or phenyl group is optionally substituted with hydroxy, $(C_3\text{-}C_8)$cycloheteroalkyl, $-CON\ R^{18}(CH_2)_pNR^{20}R^{21}$, $-(CH_2)_p\text{-}(CHR^{22})_m\text{-}(CH_2)_n\text{-}NR^{20}R^{21}$, or $-(CH_2)_p\text{-}(CHR^{22})_m\text{-}(CH_2)_n\text{-}NR^{20}R^{21}$, wherein p is 0-5, m is 0-5, n is 0-5, R^{22} is hydroxy or $(C_1\text{-}C_6)$alkyl, and

R^{20} and R^{21} are each, independently selected from:

(a) H, $(C_1\text{-}C_{12})$alkyl, $(C_3\text{-}C_{12})$cycloalkyl, $(C_3\text{-}C_{10})$heterocycloalkyl, $(C_6\text{-}C_{10})$aryl, $(C_5\text{-}C_9)$heteroaryl, $(C_1\text{-}C_6)$alkyl$(C_6\text{-}C_{12})$aryl, wherein said groups are optionally substituted by one or more hydroxy, halo, amino, trifluoromethyl, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$alkyl$(C_3\text{-}C_{10})$heterocycloalkyl, or $(C_1\text{-}C_6)$alkyl$(C_6\text{-}C_{10})$aryl; or

(b) $NR^{20}R^{21}$ taken together represent hydrogen, morpholine, or 4-$(C_1\text{-}C_6)$ alkylpiperizine;

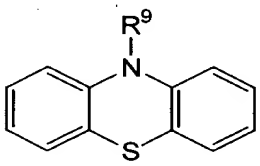
R^6 is

(a) $(C_1\text{-}C_6)$alkyl or $(C_2\text{-}C_8)$alkenyl, each optionally substituted by one or more phenyl groups, or

(b) phenyl substituted by halo, $(C_1\text{-}C_6)$alkoxy; and

R^7 and R^8 are the same, or different, and are selected from H, nitro, $(C_1\text{-}C_6)$alkoxy, or halogen selected from fluoro, chloro, and bromo;

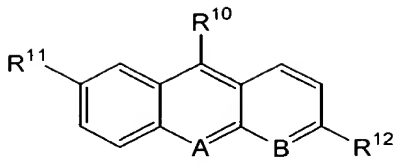
wherein, for group II,



R^9 is $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_{10})$cycloalkyl, or phenyl, wherein said alkyl, cycloalkyl or phenyl group is optionally substituted with hydroxy, $(C_3\text{-}C_8)$cycloheteroalkyl, $-CON\ R^{18}(CH_2)_pNR^{20}R^{21}$, $-(CH_2)_p\text{-}(CHR^{22})_m\text{-}(CH_2)_n\text{-}NR^{20}R^{21}$, or $-(CH_2)_p\text{-}(CHR^{22})_m\text{-}(CH_2)_n\text{-}NR^{20}R^{21}$, wherein p is 0-5, m is 0-5, n is 0-5, R^{22} is hydroxy or $(C_1\text{-}C_6)$alkyl, and

R^{20} and R^{21} are each independently selected from H, $(C_1\text{-}C_{12})$alkyl, $(C_3\text{-}C_{12})$cycloalkyl, $(C_3\text{-}C_{10})$heterocycloalkyl, $(C_6\text{-}C_{10})$aryl, $(C_5\text{-}C_9)$heteroaryl, $(C_1\text{-}C_6)$alkyl$(C_6\text{-}C_{12})$aryl, wherein said groups are optionally substituted by one or more hydroxy, halo, amino, trifluoromethyl, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$alkyl$(C_3\text{-}C_{10})$heterocycloalkyl, $(C_1\text{-}C_6)$alkyl$(C_5\text{-}C_9)$heteroaryl, or $(C_1\text{-}C_6)$alkyl$(C_6\text{-}C_{10})$aryl;

wherein, for group III,



R^{10} is $-N-R^{18}R^{19}$, where

R^{18} is H, $(C_1\text{-}C_6)$alkyl, or phenyl, and

R^{19} is H, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_{10})$cycloalkyl, or phenyl, wherein said alkyl, cycloalkyl or phenyl group is optionally substituted with hydroxy, $(C_3\text{-}C_8)$cycloheteroalkyl, $-CON\ R^{18}(CH_2)_pNR^{20}R^{21}$, $-(CH_2)_p\text{-}(CHR^{22})_m\text{-}(CH_2)_n-NR^{20}R^{21}$, or $-(CH_2)_p\text{-}(CHR^{22})_m\text{-}(CH_2)_n-NR^{20}R^{21}$, wherein p is 0-5, m is 0-5, n is 0-5, R^{22} is hydroxy or $(C_1\text{-}C_6)$alkyl, and

R^{20} and R^{21} are each, independently selected from:

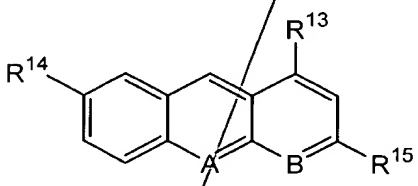
(a) H, $(C_1\text{-}C_{12})$alkyl, $(C_3\text{-}C_{12})$cycloalkyl, $(C_3\text{-}C_{10})$heterocycloalkyl, $(C_6\text{-}C_{10})$aryl, $(C_5\text{-}C_9)$heteroaryl, $(C_1\text{-}C_6)$alkyl$(C_6\text{-}C_{12})$aryl, wherein said groups are optionally substituted by one or more hydroxy, halo, amino, trifluoromethyl, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$alkyl$(C_3\text{-}C_{10})$heterocycloalkyl, $(C_1\text{-}C_6)$alkyl$(C_5\text{-}C_9)$heteroaryl, or $(C_1\text{-}C_6)$alkyl$(C_6\text{-}C_{10})$aryl; or

(b) $NR^{20}R^{21}$ taken together represent hydrogen, morpholine, or 4-$(C_1\text{-}C_6)$ alkylpiperizine;

A and B are the same or different, and each represents carbon or nitrogen; and

R^{11} and R^{12} are the same, or different, and are selected from H, nitro, $(C_1\text{-}C_6)$alkoxy, or halogen selected from fluoro, chloro, and bromo;

wherein, for group IV,



R^{13} is $-N-R^{18}R^{19}$, where

R^{18} is H, $(C_1\text{-}C_6)$alkyl, or phenyl, and

R^{19} is H, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_{10})$cycloalkyl, or phenyl, wherein said alkyl, cycloalkyl or phenyl group is optionally substituted with hydroxy, $(C_3\text{-}C_8)$cycloheteroalkyl, $-CON\ R^{18}(CH_2)_pNR^{20}R^{21}$, $-(CH_2)_p\text{-}(CHR^{22})_m\text{-}(CH_2)_n-NR^{20}R^{21}$, or

$-(CH_2)_p-(CHR^{22})_m-(CH_2)_n-NR^{20}R^{21}$, wherein p is 0-5, m is 0-5, n is 0-5, R^{22} is hydroxy or (C_1-C_6)alkyl, and

R^{20} and R^{21} are each, independently selected from:

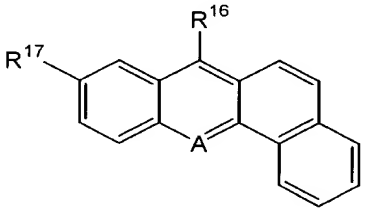
(a) H, (C_1-C_{12})alkyl, (C_3-C_{12})cycloalkyl, (C_3-C_{10})heterocycloalkyl, (C_1-C_6)alkyl(C_5-C_9)heteroaryl, (C_5-C_9)heteroaryl, (C_6-C_{10})aryl, and (C_1-C_6)alkyl(C_6-C_{10})aryl, wherein said groups are optionally substituted by one or more hydroxy, halo, amino, trifluoromethyl, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)alkyl(C_3-C_{10})heterocycloalkyl, (C_1-C_6)alkyl(C_5-C_9)heteroaryl and (C_1-C_6)alkyl(C_6-C_{10})aryl; or

(b) $NR^{20}R^{21}$ taken together represent hydrogen, morpholine, or 4-(C_1-C_6) alkylpiperizine;

A and B are the same or different, and each represents carbon or nitrogen; and

R^{14} and R^{15} are the same, or different, and are selected from H, nitro, (C_1-C_6)alkoxy, or halogen selected from fluoro, chloro, and bromo; and

wherein, for group V,



A is carbon or nitrogen;

R^{16} is $-N-R^{18}R^{19}$, where

R^{18} is H, (C_1-C_6)alkyl, or phenyl, and

R^{19} is H, (C_1-C_6)alkyl, (C_3-C_{10})cycloalkyl, or phenyl, wherein said alkyl, cycloalkyl or phenyl group is optionally substituted with hydroxy, (C_3-C_8)cycloheteroalkyl, $-CON\ R^{18}(CH_2)_pNR^{20}R^{21}$, $-(CH_2)_p-(CHR^{22})_m-(CH_2)_n-NR^{20}R^{21}$, or $-(CH_2)_p-(CHR^{22})_m-(CH_2)_n-NR^{20}R^{21}$, wherein p is 0-5, m is 0-5, n is 0-5, R^{22} is hydroxy or (C_1-C_6)alkyl, and

R^{20} and R^{21} are each, independently selected from:

(a) H, (C_1-C_{12})alkyl, (C_3-C_{12})cycloalkyl, (C_3-C_{10})heterocycloalkyl, (C_6-C_{10})aryl, (C_5-C_9)heteroaryl, (C_1-C_6)alkyl(C_6-C_{10})aryl, and (C_1-C_6)alkyl(C_5-C_9)heteroaryl, or wherein said groups are optionally substituted by one or more hydroxy, halo, amino, trifluoromethyl, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)alkyl(C_3-C_{10})heterocycloalkyl, (C_1-C_6)alkyl(C_5-C_9)heteroaryl, or (C_1-C_6)alkyl(C_6-C_{10})aryl; or